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EXAMINER
SCHWADRON, R

ART UNIT	PAPER NUMBER
1816	6

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JACOBSON PRICE HOLMAN & STERN
THE JENIFER BUILDING
400 SEVENTH STREET NW
WASHINGTON DC 20004

DATE MAILED: 08/22/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-12 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-12 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☒ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☒ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

15. Claims 1-12 are under consideration.

16. Drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

17. This application contains sequence disclosures (eg. on pages 11,12 and 14) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). In no case may an applicant extend the period for response beyond the SIX MONTH statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

18. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
The declaration in the instant application needs to claim priority to PCT/DK94/00318 under 35 U.S.C. § 120 because said application is a CIP of PCT/DK94/00318.

19. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph,

as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to use the claimed method or autovaccine for the treatment of disease in vivo in humans. The claimed autovaccines read on autovaccines for the treatment of human disease. Regarding the claimed method, the specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the use for the instant invention disclosed in specification is the treatment of disease in vivo in humans. The state of the art is such that is unpredictable from the in vivo mouse data disclosed in the specification as to whether the claimed inventions could be used for the treatment of human disease.

Regarding the mouse data disclosed in the specification, Osband et al. teaches that there exists a lack of useful animal models that can be applied to immunotherapy. Osband et al. further teach that animal models are not generally predictive of therapeutic efficacy in humans as relates to immunotherapy regimens (see page 193 in particular).

Regarding the use of peptides or proteins for therapeutic purposes (which are encompassed by the claimed method as disclosed in the specification), pharmaceutical therapies in the absence of appropriate in vivo or in vitro data establishing that said peptides can be used for the treatment of humans are unpredictable for the following reasons; (1) the peptide/protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently

short half-life of the protein/peptide; (2) the peptide/protein may not reach the target area because, i.e. the protein/protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein/peptide has no effect; and (3) other functional properties, known or unknown, may make the peptide/protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat. App. and Inter. 1992).

There is no disclosure in the specification of an actual autovaccine suitable for the treatment of human disease or guidance as to how such an autovaccine would be made. Regarding page 18 of the specification, there is no guidance in the specification as how a human TNFalpha autovaccine would be made. There is no guidance in the specification as to where T cell epitopes could be inserted in human TNFalpha without disrupting the overall tertiary structure. There is no guidance in the specification as to what dosage of any particular agent needs to be administered in order to treat any particular human disease or guidance as to how such a dosage would be established. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

20. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in the recitation of "modulation of self-proteins" because it is unclear what this means or

encompasses. Claim 1 is indefinite in the recitation of "modulated self-protein" because it is unclear what this means or encompasses and it lacks antecedent basis within the claim. Claim 1 is indefinite in the recitation of "providing a self-portion by molecular biological means" because it is unclear what this means or encompasses. Claim 2 is indefinite in the recitation of "preserve flanking regions" because it is unclear what this means or encompasses. Claim 6 is indefinite in the recitation of "modulated" because it is unclear what this means or encompasses. Claim 8 is indefinite in the recitation of "e.g. cancer patients" because it is unclear what this means or encompasses. Claim 11 is substantially duplicative of claim 10 because the recitation of an intended use carries no patentable weight in this product claim and therefore the two claims read on the same product.

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 1-7,9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowenadler et al. in view of Berzofsky et al., Hellman (WO 93/05810) and Etlinger.

The claims are drawn to a method for the modulation of self proteins. Lowenadler et al. teach that a T helper cell epitope of

16 amino acids can be inserted into a chimeric protein and induce an increased antibody response against the chimeric protein (see abstract). Lowenadler et al. teaches that the T helper cell epitope is inserted in a location that would be expected to preserve the tertiary structure of the chimeric protein (eg. see Figure 1). Berzofsky et al. teach that most antibodies against intact proteins bind conformational epitopes that are determined by the three dimensional structure induced by the tertiary structure of said protein (see page 177). Therefore, a routineer would have inserted the T cell epitope in such a manner as to not disturb the tertiary structure of the protein. The construct taught by Lowenadler et al. is made by molecular biologic means and has at least 4 amino acids of the original protein on either side of the T cell epitope (see page 1186). Lowenadler et al. do not teach that this procedure is specifically used for modulation of self proteins. Hellman teaches that modulation of self proteins can be achieved using self-protein conjugated to a carrier which is recognized by T helper cells wherein the self protein is IgE (see pages 5-12). Hellman teaches that it is desirable to modulate the presence of IgE in patients that suffer from allergies (see abstract). Hellman teaches that the autovaccine (self-protein conjugated to a carrier which is recognized by T helper cells) can contain an adjuvant (page 11, second paragraph). A routineer would have used any art known adjuvant suitable for human administration. A routineer would have added any art cytokine which could boost the immune response to the autovaccine. Etlinger et al. teach that T cell epitopes derived from tetanus toxoid can be used to increase antibody response against a molecule to which said epitopes are conjugated (see Abstract). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to

have created the claimed invention because Lowenadler et al. teach that by inserting T helper epitope(s) into a chimeric protein that increased antibody responses against different epitopes of the protein can be obtained. Furthermore, Lowenadler et al. shows that by increasing the number of copies of the T cell epitope placed into the chimeric protein and maximizing the location that increased antibody responses against multiple epitopes on the same chimeric protein can be achieved (see Table 1 and 1187-1188). A routineer would have used tetanus toxoid protein in the conjugate because Etlinger et al. teach the desirability of using molecules recognized by T cells that individuals would have already been vaccinated against (eg. tetanus toxoid).

23. Claims 8,10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowenadler et al. in view of Berzofsky et al., Hellman (WO 93/05810) and Etlinger as applied to claims 1-7,9 above, and further in view of prior art disclosed in the specification (page 18, last paragraph).

The claims are drawn to autovaccines containing TNFα. Paragraph 23 makes obvious the instant invention except for the use of TNFα. Hellman teaches that modulation of self proteins responsible for manifestations of a particular disease can be achieved using self-protein conjugated to a carrier which is recognized by T helper cells(see pages 5-12). The specification discloses that the role of TNFα in the pathogenesis of various diseases is known in the art (page 18, last paragraph). It would have been prima facies obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because the role of TNFα was known in the art and Hellman

teaches that modulation of self proteins responsible for manifestations of a particular disease can be achieved using self molecules that contain T helper epitopes. The recitation of an intended method of use in these product claims carries no patentable weight.

24. No claim is allowed.

25. Papers related to this application may be submitted to Group 180 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 180 at (703) 305-7939.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Tuesday through Friday from 8:30 to 6:00. The examiner can also be reached on alternative Mondays. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1816
August 16, 1996

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP 1800